MILITARY PSYCHOLOGY, 4(4), 189-190

# Preface to the Special Issue

This special issue of *Military Psychology* grew out of a symposium on the use of stimulants to ameliorate sleep loss during sustained operations, held at the 1990 annual meeting of the American Psychological Association (APA). Gerald P. Krueger (U.S. Army) and Harvey Babkoff (Bar-Ilan University) were co-chairmen for that symposium.

The impetus for the symposium stemmed from the work of the Continuous-Sustained Operations Subgroup of the U.S. Department of Defense Human Factors Engineering Technical Group headed by Gerald P. Krueger. That subgroup's concerns include issues of high workload demands on soldiers, sailors, marines, and airmen in various military operations involving long work hours, sustained performance, and significant sleep deprivation. Work demands of unique military missions, like those of special operations forces, often require almost superhuman soldierly effort. Military forces express active interest in countermeasures to fatigue, in particular the potential of stimulant drugs to maintain alertness and ameliorate effects of sleep loss to meet extended performance requirements.

Concerns with stimulant drugs include their wide-ranging and poorly understood effects on body biochemistry and physiology, and especially on performance of all types of tasks. Some stimulants distort perception, have untoward side effects, leave hangovers, can affect safety, produce rebound effects like depression and fatigue, require subsequent increased doses to produce the same effects, and are likely to be addicting.

However, significant research advances in neuroscience, psychopharmacology, and pharmacology suggest the need for concurrent behavioral and biomedical baseline work on developmental compounds that may avoid problems inherent in most currently available stimulants. Much of the research on this topic is being done by teams of psychologists and physicians in military research laboratories. The APA Division 19 symposium brought together researchers from the U.S. military services to review present military research efforts on stimulants and to coordinate future plans.

The introductory article by Harvey Babkoff and Gerald P. Krueger suggests that U.S. military researchers approach these complicated issues via two experimental paradigms: (a) sleep deprivation studies to assess performance recovery from fatigue effects after participants are administered a bolus dose of stimulant drug and (b) preventive designs in which

drugs are administered on a regular schedule in an attempt to maintain adequate performance throughout sleep-deprived sustained work periods. These authors review current research progress, point out differences in approach, and propose an experimental programmatic scheme for merging disparate projects into a joint program to address a full slate of experimental and practical variables.

Stimulant studies performed at the U.S. Army Walter Reed Army Institute of Research, directed by Gregory L. Belenky, team research psychiatrists with psychologists to test several classes of stimulants on performance recovery after sleep deprivation (see Newhouse et al.). Researchers at the U.S. Naval Aerospace Medical Research Laboratory also employ a recovery protocol, so far studying only methamphetamine (see Shappell, Neri, & DeJohn). Exploring a preventive design to maintain performance over the duration of long work sessions, scientists at the U.S. Naval Health Research Center have thus far experimented with pemoline and methylphenidate (see Babkoff et al.).

This special issue of *Military Psychology* highlights many points associated with the use of stimulants and subsequent performance. It is intended to challenge military psychologists to assist military biomedical research laboratories to program, plan, and conduct solid medical and behavioral research on alertness compounds. Answering such important military questions, especially if safe and effective alertness compounds are identified, will undoubtedly provide high payoffs for the general populace as well.

*Gerald P. Krueger*
*Guest Editor*

MILITARY PSYCHOLC

# Use of St
# Effects of

*U.S. Army I*

A variety of experim
the impact of stimul
to sleep loss and su
*preventive* (mainten
periods of time or i
sleep deprivation a
reviewed and their
practical applicatio
discussed.

Many U.S. soldiers
variety of personal r
that, at least since W
stimulants to select t
to reduce fatigue, m
tended periods of ti
reconnaissance patro
even bombing missio
are not well documen
available. It appears
porting data from th

Requests for reprints sh
Environmental Medicine,



ISSN 0899-5605

# MILITARY PSYCHOLOGY

Volume 4, Number 4, 1992


SPECIAL ISSUE:
Stimulants to Ameliorate Sleep Loss During Sustained Operations
*Gerald P. Krueger and Harvey Babkoff, Guest Editors*

MILITARY PSYCHOLOGY, 4(4), 191-205

# Use of Stimulants to Ameliorate the Effects of Sleep Loss During Sustained Performance

Harvey Babkoff
*Bar-Ilan University*

Gerald P. Krueger
*U.S. Army Research Institute of Environmental Medicine*

A variety of experimental approaches is presently under investigation to study the impact of stimulant drugs on anticipated decrements of performance due to sleep loss and sustained operations. The drugs have been used either in a *preventive* (maintenance) paradigm designed to maintain behavior over long periods of time or in a *recovery* paradigm designed to offset the effects of sleep deprivation and/or sustained performance. Several such studies are reviewed and their results evaluated. Questions concerning theoretical and practical applications are raised, and suggestions for future research are discussed.

Many U.S. soldiers in the Vietnam conflict used stimulant drugs for a variety of personal reasons (Holloway, 1974). Less well known is the fact that, at least since World War II, various military forces sporadically issued stimulants to select troops for specialized mission applications in attempts to reduce fatigue, maintain alertness, and sustain performance over extended periods of time. These applications usually involved long-range reconnaissance patrols (Jones, 1985), very long air transport flights, and even bombing missions (e.g., Senechal, 1988). However, most such usages are not well documented, and few data on their hazards or effectiveness are available. It appears that such military uses were initiated without supporting data from the scientific community, which has not provided the

Requests for reprints should be sent to Gerald P. Krueger, U.S. Army Research Institute of Environmental Medicine, Natick, MA 01760-5007.

empirical studies needed to define the wide-ranging effects of stimulants on body biochemistry and physiology, and especially on performance tasks.

The effects of sleep loss and sustained operations on behavior and performance have been the concern of the military and emergency rescue organizations whose missions include continuous operations during human conflict and natural disasters. Many studies have been performed over the past 50 years to elucidate the effects of long-term sleep deprivation, sleep disruption, and/or continuous performance on psychological, physiological, and performance variables (for extensive bibliographies, see Krueger & Barnes, 1989; Krueger, Cardenales-Ortiz, & Loveless, 1985). The data from a variety of laboratories in several countries indicate that long-term sleep deprivation results in complex changes in perceptual, cognitive, and psychomotor performance and in subjective psychological ratings. These changes have both monotonic and rhythmic components. General (monotonic) deterioration in performance occurs as a function of the amount of prior wakefulness and is accompanied by circadian rhythmic oscillations, with peaks usually occurring in midmorning and early evening and with troughs occurring at approximately 1400 to 1800 and 0200 to 0600 (Babkoff, Caspy, Mikulincer, & Sing, 1991).

Studies have also been designed to test various solutions for preventing performance decrements. The impact of remedial interventions on the decrements due to sleep loss and sustained operations is presently under investigation in several laboratories. One approach concentrates on the manipulation of sleep duration (e.g., naps) and the placement of sleep in the circadian cycle, either by a sleep management regimen (Naitoh & Angus, 1987) or as aided by a variety of quick-acting sedatives (Caldwell, Comperatore, & Shanahan, 1992; O'Donnell et al., 1988; Spinweber, 1986). Other approaches concentrate on ameliorating the negative effects of sleep deprivation by use of stimulants. A variety of research designs and stimulant drug administration protocols is represented in the studies published in this special issue of *Military Psychology* and reviewed in this article.

Intervention by stimulants has been studied by two different protocols. The drugs have been used either in a recovery paradigm designed to offset the effect of sleep deprivation and reestablish behavior already deteriorated or in a preventive (maintenance) paradigm designed to maintain behavior over long periods of time even while being sleep deprived.

Two research groups—Walter Reed Army Institute of Research (WRAIR) and Naval Health Research Center (NHRC)—recently used a combined sleep deprivation, sustained-operations design with emphasis on sleep deprivation (60 to 64 hr of sleep loss) and continuous testing and retesting on standardized cognitive tasks. One group—Naval Aerospace Medical Research Laboratory (NAMRL)—used a two-cycle, work-rest-work sustained-operations design separated by a 6-hr sleep period. Em-

phasis in this design was on the ability to continue high-level performance during sustained operations.

## WRAIR STUDIES

WRAIR researchers conducted a series of recovery paradigm experiments using a variety of stimulants and dose levels. They used a 60-hr sleep deprivation protocol to test the effects of dextro-amphetamine, nicotine, and l-deprenyl (a monoamine oxidase inhibitor) on mood, alertness (measured subjectively and objectively by the Multiple Sleep Latency Test), and performance (Newhouse et al., 1989; Newhouse et al., 1992). Subjects were deprived of sleep 48 hr prior to administration of a single dose of the drug on the morning (0800) of the third day of the study. Recovery and continued maintenance of the dependent variables were subsequently tested during the last 12 hr of the study (0800 to 2000).

The researchers reported that intravenously injected nicotine is ineffective in restoring alertness, mood, or cognitive performance. The l-deprenyl improved some aspects of performance but did not affect alertness or mood (Belenky et al., 1990; Newhouse et al., 1992). The effects of orally administered d-amphetamine, studied in a three-dose-response experiment (placebo, 5 mg, 10 mg, or 20 mg), were interesting. The authors reported that the 20-mg dose of d-amphetamine significantly increased time to fall asleep (sleep latency) and restored cognitive performance to rested baseline levels for 10 to 12 hr postdrug. Effects on subjective alertness and mood were similar but less enduring. Although normalizing performance, d-amphetamine produced a dose-dependent increase in oral temperature, with the 20-mg dose raising temperature above baseline values.

The use of a dose-response design enhanced the value of these studies and provided comprehensive information. Such designs should be encouraged in studying the psychopharmacology of stimulants on performance. The WRAIR group continues to study stimulants, including caffeine, using the same basic protocol (D. M. Penetar & G. L. Belenky, personal communication, April 14, 1992).

## NAMRL STUDIES

In the first of a planned series of experiments, the research group at NAMRL used a simulated sustained flight operations work-rest-work design to test the impact of a single dose of methamphetamine (10 mg/70 kg body weight) on maintaining mood and performance (Shappell, Neri, & DeJohn, 1992). The work-rest-work schedule began at 1800 with a 9-hr

preflight planning session followed by 4 hr of rest and a 14-hr mission. After a 6-hr sleep period, the 9-, 4-, and 14-hr work–rest–work pattern was repeated. At 4.5 hr into the second mission (i.e., 50.5 hr after beginning the protocol), one group was administered methamphetamine, whereas a second group received placebo. This simulated sustained-operations protocol is characterized by partial sleep loss and circadian desynchronosis. Methamphetamine improved performance on the Manikin (visual spatial rotation) and Pattern Recognition (spatial processing) tasks of the Unified Tri-Service Cognitive Performance Assessment Battery (see Englund et al., 1987).

The authors concluded that methamphetamine can ameliorate fatigue during sustained operations without producing euphoria; however, the study tested only one dose level of methamphetamine. Clearly, extensive subsequent testing is required to provide information on a large number of additional variables regarding its impact as a recovery agent during sustained performance.

## NHRC STUDIES

The NHRC group used a 64-hr sleep deprivation protocol to test the effects of multiple doses of a single concentration of methylphenidate or pemoline on alertness, mood, and performance (Babkoff et al., 1992). Their protocol differed from WRAIR's in that they studied the maintenance, rather than the recovery, of these dependent variables during the 64-hr sleep deprivation period. The drug was administered either on a 6-hr regimen (methylphenidate, 10 mg, 8 doses) or on a 12-hr regimen (pemoline, 37.5 mg, 4 doses) beginning at 2200 on the first night of sleep deprivation until either 1000 or 1600 on the third day. The sleep deprivation and testing continued until 2200 on the third night. They reported that methylphenidate had no systematically significant effect on mood, alertness, or performance. Pemoline, however, was significant in improving alertness and performance speed on all the cognitive tasks, but it did not affect mood as measured by the Profile of Mood States.

With regard to performance accuracy, the results were complicated. Pemoline showed a trend to maintain accuracy on some tasks, was ineffective on other tasks, and significantly exacerbated the sleep loss decrement in accuracy on a logical reasoning task. Their protocol and analysis permitted differentiating the effects of accumulated sleep loss from that of the hours-of-the-day effect (circadian cycle). The major impact of the drug occurred at the circadian nadir (0200 to 0600). This either could be caused by a selective interaction of the drug with the circadian cycle, or it could simply reflect the fact that performance is most decremented during

the circadian nadir, so that the counteracting effect of the drug is most easily measured at that point. The NHRC group has also continued to use its basic protocol to study caffeine as an antagonist to the effects of sleep deprivation (T. L. Kelly, personal communication, April 14, 1992).

## DEFINING THE THEORETICAL AND EMPIRICAL QUESTIONS

These experiments can be viewed as part of a basic and applied strategy to test the impact of stimulants on sleep loss and sustained operations. What was the rationale for which the experiments were designed and performed, and how do we best frame questions to obtain reasonable answers?

Amphetamines and other stimulants (e.g., caffeine) have been tested and used as agents to ameliorate fatigue-related decrements in behavior, mood, and performance as well as decrements associated with certain pathologies related to the central nervous system (CNS). Reports of increased well-being in a majority of subjects (Hurst, Weidner, Radlow, & Ross, 1973; Nash, 1962; Spiegel, 1979; Weiss & Laties, 1962) are potent reasons for testing amphetamines and amphetamine-related compounds as antagonists to the deleterious effects of sleep loss and fatigue on mood and performance. Furthermore, the vast information base available on the effects of amphetamines on humans and animals makes it a very important reference drug in neuropsychopharmacological research (Spiegel, 1979). Other stimulants (e.g., methylphenidate and pemoline) have been shown to enhance performance in tedious discrimination or rote learning tasks for children suffering from attention deficit disorder (Peloquin & Klorman, 1986; Rapoport et al., 1980; R. H. Rosenthal & Allen, 1978), in fatigued normal subjects (Gelfand, Clark, Herbert, Gelfand, & Holmes, 1968), and in narcoleptics (Mitler, Shafor, Hajdukovich, Timms, & Browman, 1986). These effects have been attributed to an enhancement of attention, increased motivation, or reduced impulsiveness (Douglas, 1983; R. H. Rosenthal & Allen, 1978; Stroufe, 1975). Amphetamine, pemoline, methylphenidate, and caffeine increase sleep latencies (Mitler et al., 1986; Zwyghuizen-Doorenbos, Roehrs, Lipshutz, Timms, & Roth, 1990). Caffeine improved auditory vigilance reaction time (RT) even after a restricted sleep of 5 hr (L. Rosenthal, Roehrs, Zwyghuizen-Doorenbos, Plath, & Roth, 1991).

Based on these findings, it makes sense to test a variety of drugs with stimulant-like properties as antagonists to performance decrements during sleep loss. The research questions raised in this scientific paradigm include: Can stimulants be used effectively to maintain speedy and accurate performance during periods of sleep loss and/or sustained performance? If so, which stimulants should be used, and how can they be used most

effectively? Allied to these practical considerations are the empirical questions: How and where in the CNS do the stimulants act to ameliorate the effects of sleep loss? Can the use of stimulants help clarify the mechanisms that cause decrements in performance during sleep loss?

To answer these questions, we must establish criteria for deciding whether to use a stimulant or not and choose appropriate experimental protocols capable of providing the necessary information to make such decisions. One of the most important decisions in designing the experimental protocol relates to the tasks chosen and possible analyses of performance. For example, if the protocol is designed to study the effect of drugs in maintaining or recovering efficient behavior during prolonged sleep deprivation, then the performance tasks chosen should (a) be sensitive to the effects of sleep loss and/or sustained operations and (b) provide information on response accuracy and response speed. The effects of sleep loss and/or sustained operations should be evident and clearly marked as degraded performance in the placebo group. The drug can then be ranked according to the following forms of action on the performance measurement: (a) recovers (or maintains) response speed and response accuracy, (b) recovers (or maintains) response speed but not response accuracy, (c) does not recover (or maintain) response speed but does recover (or maintain) response accuracy, or (d) does not recover (or maintain) response speed or accuracy. In addition, the drug may (a) recover (or maintain) response speed but worsen response accuracy, (b) worsen response speed but recover (or maintain) response accuracy, or (c) worsen both response speed and accuracy. Of course, it is also possible that the drug could improve either or both of the dependent measures over baseline (i.e., non-sleep-deprived) performance. Such a finding would certainly be of interest but has not been reliably reported to date.

Newhouse et al. (1989, 1992) reported that a 20-mg dose of amphetamine was significantly effective in recovering accuracy on Serial Add/Subtract and Logical Reasoning tasks with a similar trend on the Four-Choice Reaction-Time Task. Response speed was significantly recovered on the Four-Choice Reaction-Time Task, and a similar trend was found on the Serial Add/Subtract Task. There were no reports of any synergistic interaction between amphetamine and sleep deprivation resulting in poorer performance in the drug group than in the placebo group. Nevertheless, the authors caution against generalizing from their results and do not recommend administration of amphetamines under field conditions because of possible long-term effects of the stimulant and because of significant effects of the 20-mg dose on cardiovascular variables (e.g., blood pressure and pulse).

The report by Babkoff et al. (1992) described a drug (pemoline) that may influence a variety of performance tasks during sleep loss in one of three

ways: (a) by maintaining both response speed and accuracy, (b) by maintaining response speed but being ineffective with respect to response accuracy, or (c) by maintaining response speed but worsening response accuracy. The picture presented is complicated, but it is exactly the kind of analysis that permits a rational decision regarding the type and quantity of the drug required to offset the effects of sleep loss. How useful is a drug that maintains response speed but may not maintain performance accuracy and may even exacerbate it? Ranking the forms of interaction by the drug with performance measurements may provide the information necessary to answer the question: Does the stimulant effectively maintain speedy and accurate performance?

No firm answer is currently available to the question of whether pemoline should be prescribed as an agent capable of maintaining performance (Babkoff et al., 1992). The complicated effect of pemoline on response accuracy certainly justifies further investigation. First, because one of the possible explanations for the complicated picture is a high systemic accumulation of the drug due to the multidose schedule, there is a clear need for a thorough pharmacokinetic evaluation of pemoline.

Second, there is also the problem of differences between the maintenance and the recovery protocols. No experiment has directly compared the use of a stimulant to maintain, as opposed to recover, performance during sleep loss. There may be basic differences in the impact of a drug on performance that arise from the two modes of administration. A single dose may be more effective than multiple doses in counteracting the decrement in performance, or vice versa. Newhouse et al. (1989, 1992) reported that single doses of amphetamine administered in a recovery protocol tended to enhance both response speed and performance. A single dose of pemoline administered after 48 hr without sleep might have a unidirectional antagonistic effect against decrements in speed and accuracy, although it produces a complicated picture in a multidose preventive protocol.

Third, there is a definite need to measure the blood concentration of the drug during testing sessions. A blood level-performance relationship might reduce the variance due to individual differences in drug absorption and provide clearer information on the impact of the drug on performance during sleep deprivation.

## TESTING PROCEDURES

Physiological and performance data generated during long-term sleep deprivation are influenced by both monotonic (continued sleep deprivation) and rhythmic (circadian cycle) components (Babkoff et al., 1991; Minors & Waterhouse, 1981; Monk et al., 1985). The importance of designing sleep

deprivation experiments and of analyzing data to allow separation and analysis of the monotonic and rhythmic components is discussed in detail elsewhere (Babkoff et al., 1991). One of the points raised regarding data interpretation (Babkoff et al., 1991) is the use of a protocol designed around an integral number of circadian cycles (e.g., 24 hr, 48 hr, or 72 hr). The larger the number of complete circadian cycles in a sleep deprivation protocol, the easier it is to separate the monotonic trend from the rhythmic components and obtain a stable estimate of each. In studying the effect of stimulants on performance during sleep deprivation, the protocol should, consequently, allow for analyzing the monotonic and rhythmic factors of performance and the impact of the drug on each component separately.

The maintenance protocol and data analysis used by the NHRC group revealed the importance of the circadian cycle in the impact of the stimulant on performance during long-term sleep deprivation. If one addressed this issue in a recovery protocol with a single administration of a drug (like WRAIR's), it would be necessary to expand the experiment from 60 hr (e.g., Newhouse et al., 1989) to 72 hr. The initial effect of baseline sleep loss can, then, be assessed during two 24-hr cycles prior to the administration of the drug. This period would then be followed by a complete 24-hr cycle after drug administration. Thus, the impact of the drug should be tested as a recovery agent not only against the effects of hours of prior wakefulness but also against the effects of the circadian rhythm.

The data from the NHRC multidose maintenance protocol using pemoline imply that the most significant impact occurs when the drug is administered so that the presumed peak blood levels coincide with the circadian nadir. These data raise the important issue of the chronopharmacology, or time of administration of a drug, especially in a single-dose recovery protocol. At what time during the circadian cycle should the drug be administered? The time of administration of a single dose of stimulant could be a crucial variable in determining the impact of the drug on performance. This issue has yet to be studied systematically.

Another question not yet adequately addressed by the experimental protocols relates to the problem of day-to-day carryover or rebound of the drugs after the immediate, acute situation (sleep deprivation or sustained performance) has passed. This problem may be of even greater relevance when a multidose maintenance paradigm is used. How long after terminating the sleep deprivation does the drug remain act[illegible] After termination of a long session of sustained performance, can the individual who received the stimulant expect recovery sleep? Does the stimulant have a rebound effect? That is, will an individual who maintained performance with stimulants during long periods of sleep loss be "sleepier" after terminating the stimulant than one who did not use stimulants? Does recovery sleep serve the same purpose in returning performance to predeprivation levels in

individuals who received stimulants compared to those who did not receive stimulants? To date, protocols have not allowed for sufficient continued testing after termination of sleep deprivation to be able to answer these questions.

## EXPERIMENTAL TASKS

Many tasks in the performance batteries used in the studies reviewed in this article have been used previously in a number of sleep deprivation studies. Such a choice of tasks adds to a large performance database and provides the opportunity to compare performance decrement data of the sleep-deprived control group to the data of earlier studies. This enhances the reliability and validity of the drug findings when they affect these decrements. Many of the tasks generally used in studies of sleep deprivation and sustained operations were not originally designed to elucidate the point of impact of a modifying variable, and certainly not the "site of action" of an intervention such as a drug. Such considerations, however, have been important in the choices of tasks in studying the impact of drugs on performance.

Several recent drug-performance studies have been designed around the additive factors method discussed by Sternberg (1969), which divides the reaction process into discrete, separable stages—stimulus evaluation and response selection. The procedure uses a combination of event-related potential (ERP) latencies and reaction time to test the theoretical point of impact of the drug in a choice reaction-time task. A manipulation of drug that affects ERP latencies and reaction time is understood to interact with earlier stimulus evaluation mechanisms. A manipulation of drug that affects reaction time alone, but does not affect ERP latency, is understood to interact with the later response selection mechanisms. Examples of these procedures were reported by Callaway and colleagues in a series of studies over the past decade (e.g., Callaway, 1983; Halliday, Callaway, Naylor, Gratzinger, & Prael, 1986; Naylor, Halliday, & Callaway, 1985). The contingent negative variation has also been shown to be sensitive to sleep deprivation (Gauthier & Gottesmann, 1983; Naitoh, Johnson, & Lubin, 1971). The inclusion of these or similar procedures in studies of the effect of drugs on sleep deprivation and performance may aid in clarifying the underlying mechanisms and the site of the drug action.

## PROPHYLACTIC USE OF DRUGS IN SLEEP DEPRIVATION RESEARCH

Although not of direct concern to the issue reviewed here, several comments should be made regarding research into the use of short-acting hypnotics or

nonsedating sleep aids (Spinweber, 1986) to reduce the effects of sleep loss on performance. An additional approach to research into intervention techniques is prophylactic in concept and complementary to that of preparatory sleeping or napping. Can one increase the ability to withstand the effects of sleep loss by napping prior to an expected, extended period of wakefulness, and should hypnotics be used to aid in inducing such preparatory naps? The question is complicated and includes such major concerns as the type of drug, the drug dosage, the amount and quality of sleep/rest obtained, whether or not one can awaken easily during drug-induced sleep, and the possibility of increased sleep inertia (Caldwell et al., 1992; Krueger, 1989, 1991).

Several additional interesting questions may be included with regard to the quality and structure of the short-term hypnotic-induced prophylactic nap. Will sleep or naps be more or less effective as prophylactics if they consist of a higher (or lower) percentage of slow wave sleep (SWS) relative to REM sleep? It may be possible to choose selectively the structure of the sleep to be induced by a hypnotic. Pilocarpine, an orally active muscarinic cholinergic agonist, has been shown recently to promote REM sleep selectively while reducing SWS (Berkowitz, Sutton, Janowsky, & Gillin, 1990). Similar results have been found for other muscarinic cholinergic agonists, such as orally administered RS-86 (Berger, Riemann, Hochli, & Spiegel, 1989).

In contrast, drugs that bind to 5-hydroxytryptamine (serotonin) receptors increase the duration of SWS. Treatment by Ritanserin, a serotonin receptor antagonist, nearly doubled SWS (Idzikowski, Cowen, Nutt, & Mills, 1987; Idzikowski, Mills, & Glennard, 1986). Similar effects were reported with the use of the antidepressant Trazodone (Montgomery, Oswald, Morgan, & Adam, 1983). The antidepressant ORG 3770 (Metirazopine) has been reported to shorten sleep onset latency, reduce Stage 1 duration, increase Stage 3 duration, and increase REM latency.

The sleep deprivation protocols already in use could be adapted profitably to a study of the selective amplification or attenuation of certain sleep stages in preparatory napping. Such studies could provide additional information of theoretical as well as empirical interest.

Finally, the combination of prophylactic napping (either drug induced or natural) together with stimulant maintenance of performance during sleep deprivation has yet to be fully explored under experimentally controlled conditions. The often partial success of the drugs used to date may suggest that a more holistic approach to the problem of performance maintenance or recovery during sleep deprivation should be explored—an approach that includes preparatory sleep discipline together with maintenance and/or recovery treatment during long periods without sleep. Johnson, Spinweber, Gomez, and Freeman (1990) tested the effect on performance of the

combination of a hypnotic prior to sleeping followed by a stimulant upon awakening, but their subjects were not sleep deprived. We suggest that such a combination of prophylactic sleeping followed by long-term sleep deprivation with a stimulant intervention may prove to be a fruitful source of information.

## APPLICATION OF STUDIES TO FIELD USE

All of the research protocols used to date have imposed the drug dose and the time and frequency of administration according to a schedule determined by the investigator. Such rigidly controlled doses and schedules are clearly necessary when the effect of the drug is tested in a group comparison design requiring equivalence among a variety of variables and subjects. However, the field use of a drug (or drugs) may likely involve self-administration determined by individuals according to their subjective feelings of fatigue, exhaustion, and malaise due to sleep loss and the demands of sustained performance. It could be very informative to study individual use of stimulants at times and doses (within limits) determined by each subject. In such a study, each subject would, of necessity, be his or her own control, and intra-individual comparisons over time would be the major focus rather than comparisons across groups. Such a design, however, has the liability of requiring a large number of subjects and might be quite expensive.

Continuous operations may extend for periods of 10 to 20 days or longer. The long-term (chronic) effects of the use of any stimulant must also be considered and studied carefully. Stimulants may not be the only drug available for field use by soldiers. The combination of stimulants with other drugs must be tested. In addition, the interaction of stimulants with a variety of workload and environmental variables must be considered; among these variables are differing levels of cognitive and physical work requirements, ambient temperature, altitude, air pressure, and humidity.

## SUMMARY

The current state of knowledge regarding stimulants, fatigue, sleep loss, performance, and behavior is mixed. There is both "bad news" and "good news." The bad news is that, to date, there has not been a coordinated effort to use the same experimental testing procedures and drugs across laboratories engaged in sustained performance and sleep loss research. Consequently, it is not yet possible to make comprehensive summary statements about the use of stimulants as agents antagonistic to the decrements in

performance induced by sleep loss and fatigue. What is missing is a general research paradigm that can provide information on (a) a large variety of stimulants, (b) their dose-response relations to human performance and physiological variables, (c) their human pharmacokinetics under the dose regimes tested, and (d) their chronopharmacology (i.e., the relation of drug action to time of administration).

The good news is that the variety of protocols tested to date have produced reliable data on the effects of sustained operations, sleep loss, and the impact of stimulant drugs. All of the studies are designed to yield information on psychological, performance, and electrophysiological variables. Thus, the components for building a paradigm for extended studies on the impact of drugs on humans prior to, during, and after sleep deprivation and/or sustained performance are available. The establishment of an agreed upon, standardized paradigm for testing drugs with stimulant properties in sleep deprivation/sustained-operations experiments, including both a preventive and recovery regimen, would greatly enhance the possibility of determining reasonable operational recommendations regarding the use of these drugs. In addition, such standardization would permit the comparison of the older stimulants with newer drugs, such as Modafinil (Lyons & French, 1991), and with future drugs.

The purpose of this article is not to advise the military to use stimulants alone or in combination with any other drugs to maintain or enhance performance. Rather, the purpose is to clarify the type of systematic, theoretical and empirical research necessary to obtain information needed for rational and intelligent decisions regarding the use of drugs by the military. We summarized the results of ongoing research, suggested the types of questions that should be asked, the types of drug effects that should be investigated, the kind of paradigm to be used to obtain appropriate answers, and finally the criteria that a drug or combination of drugs must meet to be considered as a candidate for field use.

## ACKNOWLEDGMENTS

The authors thank Dr. Paul Naitoh of the U.S. Naval Health Research Center for a critical reading of this article and for his suggestions on improvements.

This article and the articles in this special issue of *Military Psychology* were presented in abbreviated form at a Division 19 symposium, "Stimulants to Ameliorate Sleep Loss During Sustained Operations: A Review of the Issues," on August 13, 1990, at the 98th annual meeting of the American Psychological Association, Boston. Gerald P. Krueger and Harvey Babkoff were the co-chairmen for that symposium.

## REFERENCES

Babkoff, H., Caspy, T., Mikulincer, M., & Sing, H. C. (1991). Monotonic and rhythmic influences: A challenge for sleep deprivation research. *Psychological Bulletin, 109,* 411-428.

Babkoff, H., Kelly, T. L., Matteson, L. T., Gomez, S. A., Lopez, A., Hauser, S., Naitoh, P., & Assmus, J. (1992). Pemoline and methylphenidate: Interaction with mood, sleepiness, and cognitive performance during 64 hours of sleep deprivation. *Military Psychology, 4,* 235-265.

Belenky, G. L., Penetar, D. M., Thorne, D. R., Sing, H. C., Fertig, J. B., Thomas, M. L., McCann, U. D., Schelling, A. S. D., & Newhouse, P. A. (1990, August). Stimulants in continuous operations. In G. P. Krueger & H. Babkoff (Chairs), *Stimulants to ameliorate sleep loss and sustained operations: A review of the issues.* Symposium conducted at the 98th annual meeting of the American Psychological Association, Boston.

Berger, M., Riemann, D., Hochli, D., & Spiegel, R. (1989). The cholinergic rapid eye movement sleep induction test with RS-86. *Archives of General Psychiatry, 46,* 421-428.

Berkowitz, A., Sutton, L., Janowsky, D. S., & Gillin, J. C. (1990). Pilocarpine, an orally active muscarinic cholinergic agonist, induces REM sleep and reduces delta sleep in normal volunteers. *Psychiatry Research, 33,* 113-119.

Caldwell, J. W., Comperatore, C. A., & Shanahan, D. F. (1992). *Triazolam and Temazepam: Issues and concerns relevant to the Army aviation community* (USAARL Tech. Rep. No. 92-23). Fort Rucker, AL: U.S. Army Aeromedical Research Laboratory.

Callaway, E. (1983). The pharmacology of human information processing. *Psychophysiology, 20,* 359-370.

Douglas, V. I. (1983). Attentional and cognitive problems. In M. Rutter (Ed.), *Developmental neuropsychiatry* (pp. 280-329). New York: Guilford.

Englund, C. E., Reeves, D. L., Shingledecker, C. A., Thorne, D. R., Wilson, K. P., & Hegge, F. W. (1987). *Unified Tri-Service Cognitive Performance Assessment Battery (UTC-PAB). I. Design and specification of the battery* (NHRC Tech. Rep. No. 87-10). San Diego: U.S. Naval Health Research Center.

Gauthier, P., & Gottesmann, C. (1983). Influence of total sleep deprivation on event-related potentials in man. *Psychophysiology, 20,* 351-354.

Gelfand, S., Clark, L. D., Herbert, E. W., Gelfand, D. M., & Holmes, E. D. (1968). Magnesium pemoline: Stimulant effects on performance of fatigued subjects. *Clinical Pharmacology and Therapy, 9,* 56-60.

Halliday, R., Callaway, E., Naylor, H., Gratzinger, P., & Prael, R. (1986). The effects of stimulant drugs on information processing in elderly adults. *Journal of Gerontology, 41,* 748-757.

Holloway, W. C. (1974). Epidemiology of heroin dependency among soldiers in Vietnam. *Military Medicine, 139,* 108-113.

Hurst, P. M., Weidner, M. F., Radlow, R., & Ross, S. (1973). Drugs and placebos: Drug guessing by normal volunteers. *Psychological Reports, 33,* 683-694.

Idzikowski, C., Cowen, P. J., Nutt, D., & Mills, F. J. (1987). The effects of chronic Ritanserin treatment on sleep and the neuroendocrine response to L-tryptophan. *Psychopharmacology, 93,* 416-420.

Idzikowski, C., Mills, F. J., & Glennard, R. (1986). 5-Hydroxytryptamine-2 antagonist increases human slow wave sleep. *Brain Research, 378,* 164-168.

Johnson, L. C., Spinweber, C., Gomez, S., & Freeman, C. (1990). Benzodiazepines and caffeine: Effect on daytime sleepiness, performance and mood. *Psychopharmacology, 101,* 160-167.

Jones, F. D. (1985). Sanctioned use of drugs in combat. In P. Picht, P. Berner, R. Wolf, & K. Thau (Eds.), *Psychiatry: The state of the art, Vol. 6* (pp. 489-494). New York: Plenum.

Krueger, G. P. (1989). Sustained work, fatigue, sleep loss and performance: A review of the issues. *Work and Stress, 3,* 129-141. (DTIC No. AD: A215-234)

Krueger, G. P. (1991). Sustained military performance in continuous operations: Combatant fatigue, rest and sleep needs. In R. Gal & A. D. Mangelsdorff (Eds.), *Handbook of military psychology* (pp. 255-277). London: Wiley. (DTIC No. AD: A242-507)

Krueger, G. P., & Barnes, S. M. (1989). *Human performance in continuous/sustained operations and the demands of extended work/rest schedules: An annotated bibliography—Vol. II* (USAARL Tech. Rep. No. 89-8). Fort Rucker, AL: U.S. Army Aeromedical Research Laboratory. (DTIC No. AD: A210-504)

Krueger, G. P., Cardenales-Ortiz, L., & Loveless, C. A. (1985). *Human performance in continuous/sustained operations and the demands of extended work/rest schedules: An annotated bibliography* (WRAIR Tech. Rep. No. BB-85-1). Washington, DC: Walter Reed Army Institute of Research. (DTIC No. AD: A155-619)

Lyons, T. J., & French, J. (1991). Modafinil: The unique properties of a new stimulant. *Aviation, Space, and Environmental Medicine, 62,* 432-435.

Minors, D. S., & Waterhouse, J. M. (1981). *Circadian rhythms and the human.* London: Wright PSG.

Mitler, M. M., Shafor, R., Hajdukovich, R., Timms, R. M., & Browman, C. P. (1986). Treatment of narcolepsy: Objective studies on methylphenidate, pemoline and protriptyline. *Sleep, 9,* 260-264.

Monk, T. H., Fookson, J. E., Kream, J., Moline, M. L., Pollak, C. P., & Weitzman, M. B. (1985). Circadian factors during sustained performance: Background and methodology. *Behavior Research Methods, Instruments and Computers, 17,* 19-26.

Montgomery, I., Oswald, I., Morgan, K., & Adam, K. (1983). Trazodone enhances sleep in subjective quality but not in objective duration. *British Journal of Clinical Pharmacology, 16,* 139-144.

Naitoh, P., & Angus, R. G. (1987). *Napping and human functioning during prolonged work* (NHRC Tech. Rep. No. 87-21). San Diego: U.S. Naval Health Research Center. (DTIC No. AD: A190-228)

Naitoh, P., Johnson, L. C., & Lubin, A. (1971). Modification of surface negative slow potential (CNV) in the human brain after total sleep loss. *Electroencephalography and Clinical Neurophysiology, 30,* 17-22.

Nash, H. (1962). Psychologic effects of amphetamines and barbiturates. *Journal of Nervous and Mental Disease, 134,* 203-217.

Naylor, H., Halliday, R., & Callaway, E. (1985). The effect of methylphenidate on information processing. *Psychopharmacology, 86,* 90-95.

Newhouse, P. A., Belenky, G., Thomas, M., Thorne, D., Sing, H. C., & Fertig, J. (1989). The effects of d-amphetamine on arousal, cognition, and mood after prolonged total sleep deprivation. *Neuropsychopharmacology, 2,* 153-164.

Newhouse, P. A., Penetar, D. M., Fertig, J. B., Thorne, D. R., Sing, H. C., Thomas, M. L., Cochran, J. C., & Belenky, G. L. (1992). Stimulant drug effects on performance and behavior after prolonged sleep deprivation: A comparison of amphetamine, nicotine, and deprenyl. *Military Psychology, 4,* 207-233.

O'Donnell, V. M., Balkin, T. J., Andrade, J. R., Simon, L. M., Kamimori, G. H., Redmond, D. P., & Belenky, G. L. (1988). Effects of Triazolam on performance and sleep in a model of transient insomnia. *Human Performance, 1,* 145-160.

Peloquin, L. J., & Klorman, R. (1986). Effects of methylphenidate on normal children's moods, event-related potentials and performance in memory scanning and vigilance. *Journal of Abnormal Psychology, 95,* 88-98.

Rapoport, J. L., Buchsbaum, M. S., Weingartner, H., Zahn, T. P., Ludlow, C., & Mikkelsen, E. T. (1980). Dextroamphetamine: Its cognitive and behavioral effects in normal and hyperactive boys and men. *Archives of General Psychiatry, 137,* 933-943.

Rosenthal, L., Roehrs, T., Zwyghuizen-Doorenbos, A., Plath, D., & Roth, T. (1991). Alerting effects of caffeine after normal and restricted sleep. *Neuropsychopharmacology, 4*, 103-108.

Rosenthal, R. H., & Allen, T. W. (1978). An examination of attention, arousal and learning dysfunctions of hyperkinetic children. *Psychological Bulletin, 85*, 689-715.

Senèchal, P. K. (1988). Flight surgeon support of combat operations at RAF Upper Heyford. *Aviation, Space and Environmental Medicine, 59*, 776-777.

Shappell, S. A., Neri, D. F., & DeJohn, C. A. (1992). Simulated sustained flight operations and performance, part 2: Effects of dextro-methamphetamine. *Military Psychology, 4*, 267-287.

Spiegel, R. (1979). Effects of amphetamines on performance and on polygraphic sleep parameters in man. In P. Passouant & I. Oswald (Eds.), *Pharmacology of the states of alertness* (pp. 189-201). Oxford, England: Pergamon.

Spinweber, C. L. (1986). *Sedating and nonsedating sleeping aids in air operations* (NHRC Tech. Rep. No. 86-18). San Diego: U.S. Naval Health Research Center.

Sternberg, S. (1969). The discovery of processing stages: Extensions of Donders' method. *Acta Psychologica, 30*, 276-315.

Stroufe, L. A. (1975). Drug treatment of children with behavior problems. In F. Horowitz (Ed.), *Review of child development research IV* (pp. 347-407). Chicago: University of Chicago Press.

Weiss, B., & Laties, V. G. (1962). Enhancement of human performance by caffeine and the amphetamines. *Pharmacological Review, 14*, 1-36.

Zwyghuizen-Doorenbos, A., Roehrs, T., Lipshutz, L., Timms, V., & Roth, T. (1990). Effects of caffeine on alertness. *Psychopharmacology, 100*, 36-39.